PRC LAWS AND REGULATIONS

Regulations on Company Establishment and Foreign Investment

The PRC Company Law (中華人民共和國公司法), as amended in 2018, applies to the establishment, operation and management of both PRC domestic companies and foreign-invested enterprises. Investment in the PRC by foreign investors are also regulated by the Foreign-Owned Enterprise Law of the PRC (中華人民共和國外資企業法) promulgated on April 12, 1986 and amended on October 31, 2000 and September 3, 2016, the Implementing Rules for the Foreign-Owned Enterprise Law of the PRC (中華人民共和國外資企業法實施細則) promulgated on December 12, 1990 and amended on April 12, 2001 and February 19, 2014, and the Interim Administrative Measures for the Record-filing of the Incorporation and Change of Foreign-invested Enterprises (外商投資企業設立及變更備案管理暫行辦法) promulgated on October 8, 2016 and amended on July 30, 2017 and June 29, 2018. Under these laws and regulations, the establishment of a wholly foreign-owned enterprise is subject to the approval of, or the filing with the MOFCOM or its local counterpart, and such wholly foreign-owned enterprises must register and file with the appropriate administrative bureau of industry and commerce.

The Foreign Investment Law of the People's Republic of China (中華人民共和國外商投資法) (the "**FIL**"), which was promulgated by the National People's Congress On March 15, 2019, and will come into effect on January 1, 2020, provides that the "foreign investment" refers to the investment activities in China carried out directly or indirectly by foreign natural persons, enterprises or other organizations ("**Foreign Investors**"), including the following: (1) Foreign Investors establishing foreign-invested enterprises in China alone or collectively with other investors; (2) Foreign Investors acquiring shares, equities, properties or other similar rights of Chinese domestic enterprises; (3) Foreign Investors investing in new projects in China alone or collectively with other investors; and (4) Foreign Investors investing through other ways prescribed by laws and regulations or the State Council. The State adopts the management system of pre-establishment national treatment and negative list for foreign investment. The "pre-establishment national treatment" refers to granting to Foreign Investors and their investments, in the stage of investment access, the treatment no less favorable than that granted to domestic investors and their investments; the "negative list" refers to special administrative measures for access of foreign investment in specific fields as stipulated by the State. The State will grant national treatment to foreign investments outside the negative list. The negative list will be released by or upon approval of the State Council. After the FIL comes into effect, the FIL will replace the Foreign-Owned Enterprise Law of the PRC.

Foreign investment in China is subject to the Catalogue for the Guidance of Foreign Investment Industries (2017 Revision) (外商投資產業指導目錄(2017年修訂)) issued on June 28, 2017 and effective from July 28, 2017, and the Special Administrative Measures for the Access of Foreign Investment (Negative List) (外商投資准入特別管理措施(負面清單)) issued on June 28, 2018 and effective from July 28, 2018, which together comprise the encouraged foreign-invested industries catalogue and the special administrative measures for the access of foreign investments to the restricted or the prohibited foreign-invested industries. The latter

sets out restrictions such as percentage of shareholding and qualifications of senior management. According to the Interim Administrative Measures for the Record-filing of the Incorporation and Change of Foreign-invested Enterprises, foreign investments that are not subject to special access administrative measures are only required to complete an online filing with the MOFCOM or its local counterpart. The Catalogue of Industries in which Foreign Investment is Encouraged (2019 Revision), or the 2019 Catalogue, and the Special Administrative Measures for the Access of Foreign Investment (Negative List) (2019 Revision), or the 2019 Negative List, which were issued on June 30, 2019 and will come into effect on July 30, 2019, further reduced restrictions on the foreign investment. After the 2019 Catalogue and the 2019 Negative List come into effect, they will replace the Catalogue for the Guidance of Foreign Investment Industries (2017 Revision) and the Special Administrative Measures for the Access of Foreign Investment (Negative List).

According to the Regulations on Mergers and Acquisitions of Domestic Enterprises by Foreign Investors (關於外國投資者併購境內企業的規定), or the M&A Rules, jointly promulgated by MOFCOM, the State-Owned Assets Supervision and Administration Commission of the State Council, the SAT, the State Administration for Industry and Commerce, the China Securities Regulatory Commission, and the SAFE on August 8, 2006, which became effective on September 8, 2006 and was amended by MOFCOM on June 22, 2009, a foreign investor (1) acquiring an equity interest in a non-foreign-invested PRC enterprise or subscribing to additional shares in a non-foreign-invested PRC enterprise, (2) purchasing and operating the assets of non-foreign-invested PRC enterprises through establishment of a foreign-invested enterprise, or (3) purchasing the assets of a non-foreign-invested PRC enterprise and operating such assets through establishment of a foreign-invested enterprise with such assets must comply with the PRC laws and regulations and complete registration/filing with relevant departments. Particularly, any PRC company, enterprise or individual who try to acquire any domestic enterprise related to such company, enterprise or individual through an offshore company established or controlled by such company, enterprise or individual shall comply with relevant foreign investment industry policies and be subject to approval of the MOFCOM.

Drug Regulatory Regime

We operate our business in China through Jiangsu Alphamab under a legal regime consisting of the NPCSC, the State Council and several ministries and agencies under its authority including, among others, the NMPA, and the National Health Commission. The predecessors of NMPA and NHC are the CFDA and the NHFPC, respectively, both of which were established in accordance with the Institutional Reform Program of the State Council (國務院機構改革方案) promulgated by the NPC on March 17, 2018. The NMPA is a newly established regulatory authority responsible for registration and supervision of pharmaceutical products, cosmetics and medical equipment under the supervision of State Administration for Market Regulation, or the SAMR, a newly established institution for supervising and administrating the market in China.

The NMPA has set up the CDE and other institutions. According to the Decision of the NMPA on Adjusting the Approval Procedures under the Administrative Approval Items for Certain Drugs issued by the NMPA on March 17, 2017 and effective as from May 1, 2017, the approval for an IND should be issued by the CDE of the NMPA in the name of the NMPA.

In addition, according to the Administration of Quality of Drug Clinical Practice (GCP Administration) issued by the NMPA on August 6, 2003 and effective as from September 1, 2003 and the Opinions on Deepening the Reform of the Evaluation and Approval System and Inspiring Innovation of Drugs and Medical Devices issued by the General Office of the CPC Central Committee and the General Office of the State Council on and effective as from October 8, 2017, the institutions for drug clinical trials should establish an independent ethics committee and the clinical trial schemes are subject to examination, approval and signing with approval opinions by the ethics committee before implementation, in order to protect the rights and interests of human subjects in clinical trials. For a multi-center clinical trial conducted in the PRC, after ethical review by the leader unit of clinical trial, other member units should recognize the review results of the leader unit and should not conduct repeated review.

Pharmaceutical Product Development

In the PRC, the NMPA monitors and supervises the administration of pharmaceutical products, as well as medical devices and equipment. The local provincial medical products administrative authorities are responsible for supervision and administration of drugs within their respective administrative regions. The PRC Drug Administration Law (中華人民共和國藥品管理法) promulgated by the SCNPC in 1984, as amended in 2001, 2013 and 2015, and the Implement Measures of the PRC Drug Administration Law (中華人民共和國藥品管理法實施條例) promulgated by the State Council effective in September 2002 and amended on February 6, 2016 and March 2, 2019, have laid down the legal framework for the administration of pharmaceutical products, including the research, development and manufacturing of new drugs. The PRC Drug Administration Law applies to entities and individuals engaged in the research, production, trade, application, supervision and administration of pharmaceutical products. It regulates and prescribes a framework for the administration of pharmaceutical manufactures, pharmaceutical trading companies, and medicinal preparations of medical institutions and the development, research, manufacturing, distribution, packaging, pricing and advertisements of pharmaceutical products. The Implementing Measures of the PRC Drug Administration Law serve to provide detailed implementation regulation for the PRC Drug Administration Law.

Non-Clinical Research and Animal Testing

The NMPA promulgated the Administrative Measures for Good Laboratories Practice of Non-clinical Laboratory (藥物非臨床研究質量管理規範) in 2003, which were revised on July 27, 2017, and has conducted the Administrative Measures for Good Laboratories Practice of Non-clinical Laboratory, or GLP Certification since 2003. On April 16, 2007, the NMPA issued the Circular on Measures for Certification of Good Laboratory Practice and for Non-clinical Laboratory (藥物非臨床研究質量管理規範認證管理辦法), or NMPA Circular 214, which provides that the NMPA decides whether an institution is qualified for undertaking pharmaceutical non-clinical research upon the evaluation of the institution's organizational administration, its research personnel, its equipment and facilities and its operation and management of non-clinical pharmaceutical projects. If all the requirements are met, a GLP Certification will be issued by the NMPA and the result will be published on the NMPA's website.

The State Science and Technology Commission promulgated the Regulations for the Administration of Affairs Concerning Experimental Animals (實驗動物管理條例) in November, 1988, which were amended by the State Council in January 2011, July 2013 and March 2017. The State Science and Technology Commission and the State Bureau of Quality and Technical Supervision jointly promulgated the Administration Measures on Good Practice of Experimental Animals (實驗動物質量管理辦法) in December, 1997. The State Science and Technology Commission and other regulatory authorities promulgated the Administrative Measures on the Certificate for Experimental Animals (Trial) (實驗動物許可證管理辦法(試行)) in December 2011. All of these laws and regulations require a Certificate for Use of Laboratory Animals for performing experimentation on animals.

Approval and Reform for Clinical Trials of New Drugs

According to the Administrative Measures for Drug Registration (藥品註冊管理辦法) promulgated by the NMPA in July 2007 and effective from October 1, 2007, the PRC Drug Administration Law and Implementing Measures of the PRC Drug Administration Law, new drug application is subject to clinical trials. Upon completion of non-clinical research, clinical trials must be conducted for the application of a new drug registration, and applicants must apply for approval of IND from the NMPA, or the CDE before conducting clinical trials.

The Opinions on the Reform of Evaluation and Approval System for Drugs and Medical Devices and Equipment (關於改革藥品醫療器械審評審批制度的意見), or the Reform Opinions, promulgated by the State Council on August 9, 2015 established a framework for reforming the evaluation and approval system for drugs, medical devices and equipment. The Reform Opinions indicated enhancing the standard of approval for drug registration and accelerating the evaluation and approval process for innovative drugs as well as improving the approval of drug clinical trials.

The Circular Concerning Several Policies on Drug Registration Evaluation and Approval (關於藥品註冊審評審批若干政策的公告), or the Several Policies Circular, promulgated by the NMPA on November 11, 2015 further clarified the measures and policies regarding simplifying and accelerating the approval process of drugs on the basis of the Reform Opinions. The circular further provides that the IND of new drugs is subject to one-time umbrella approval, and the procedures of declaration, review and approval by stages will no longer be adopted.

The Opinions on Encouraging the Prioritized Evaluation and Approval for Drug Innovations (關於鼓勵藥品創新實行優先審評審批的意見) promulgated by the NMPA on December 21, 2017 further clarified that a fast track IND or drug registration pathway will be available to the innovative drugs.

According to the Circular on Adjusting Evaluation and Approval procedures for Clinical Trials for Drugs (關於調整藥物臨床試驗審評審批程序的公告) promulgated by the NMPA on July 24, 2018, within 60 days after the acceptance of and the fees paid for the IND, the applicant may conduct the clinical trials for the drug in accordance with the clinical trial protocol submitted, if the applicant has not received any negative or questioning opinion from the CDE.

Therapeutic Biological Products

According to the Administrative Measures for Drug Registration, biological products shall be registered in accordance with the new drug application procedure, and according to Appendix III to the Administrative Measures for Drug Registration, the registration categories of therapeutic biological products shall be divided into 15 types:

(i) biological products not marketed in the domestic and overseas;

(ii) monoclonal antibodies;

(iii) gene therapy, somatic therapy and its products;

(iv) allergenic original products;

(v) multicomponent product with biological activity that extracted from human, animal tissues or bodily fluids, or prepared by fermentation;

(vi) new compound products consist of marketed biological products;

(vii) biological products that have been marketed abroad but have not been marketed in the domestic;

(viii) micro-ecological products containing unapproved strains;

(ix) products whose structure is not exactly the same as the marketed products and have not been marketed in the domestic and overseas (including amino acid site mutation and deletion, the generation, elimination, or alteration of post-translational modifications, chemically modify the products resulting from differences in expression systems, etc.);

(x) products which preparation method is different from that of marketed products (for example, using different expression systems, host cells, etc.);

(xi) products prepared by DNA recombination technology for the first time (for example, recombinant technology replaces synthetic technology, biological tissue extraction or fermentation technology, etc.);

(xii) the products that have not been marketed in the domestic and overseas are changed from non-injection route administration to injection route administration, or from local administration to systemic administration;

(xiii) biological products that change the dosage of marketed products but do not change the route of administration;

(xiv) biological product that changes the route of administration (not including the above 12 terms); and

(xv) biological products with national drug standards.

Drug Clinical Trial Registration

According to the Administrative Measures for Drug Registration, upon obtaining the approval of its IND and before conducting a clinical trial, an applicant shall file a registration form with the NMPA containing various details, including the clinical study protocol, the name of the principal researcher of the leading institution, names of participating institutions and researchers, an approval letter from the ethics committee, and a sample of the Informed Consent Form, with a copy sent to the competent provincial administration departments where the trial institutions will be located. The Announcement on Drug Clinical Trial Information Platform (關於藥物臨床試驗信息平台的公告) announced by the NMPA on September 6, 2013, provides that, instead of the aforementioned registration field with the NMPA, all clinical trials approved by the NMPA and conducted in China shall complete a clinical trial registration and publish trial information through the Drug Clinical Trial Information Platform. The applicant shall complete the trial pre-registration within one month after obtaining the approval of the IND in order to obtain the trial's unique registration number and complete registration of certain follow-up information before the first subject's enrollment in the trial. If the registration is not completed within one year after the approval of the IND, the applicant shall submit an explanation, and if the first submission is not completed within three years, the approval of the IND shall automatically expire.

Phases of Clinical Trials and the Communication with the CDE

According to the Administrative Measures for Drug Registration, a clinical trial consists of Phases I, II, III and IV. Phase I refers to the initial clinical pharmacology and safety evaluation studies in humans. Phase II refers to the preliminary evaluation of a drug candidate's therapeutic effectiveness and safety for particular indications in patients, to provide evidence and support for the design of Phase III clinical trials and to settle the administrative dose regimen. Phase III refers clinical trials undertaken to confirm the therapeutic effectiveness and safety on patients with target indications, to evaluate the overall benefit-risk relationships of the drug, and ultimately to provide sufficient evidence for the review of drug registration application. Phase IV refers to a new drug's post-marketing study to assess therapeutic effectiveness and adverse reactions when the drug is widely used, to evaluate the overall benefit-risk relationships of the drug when used among the general population or specific groups and to adjust the administration dose.

However, according to the Technical Guiding Principles for Clinical Trials of Anti-tumor Drugs issued by the NMPA on May 15, 2012, the clinical study staging of anti-tumor drugs is not a fixed developmental sequence. The rapid development of anti-tumor drug research theories and technologies is likely to have an impact on future anti-cancer drug development models. Therefore, applicants can actively explore more scientific and rational research methods and promptly seek advice from the drug registration department under the NMPA.

According to the Circular on Adjusting Evaluation and Approval Procedures for Clinical Trials for Drugs, where the application for clinical trial of new investigational drug has been approved, upon the completion of Phases I and II clinical trials and prior to Phase III clinical trial, the applicant shall submit the application for Communication Session to CDE to discuss with CDE the key technical questions including the design of Phase III clinical trial protocol. According to the Administrative Measures for Communication on the Research, Development and Technical Evaluation of Drugs (藥物研發與技術審評溝通交流管理辦法), or the Communication Measures, promulgated by the NMPA on September 30, 2018, during the research and development periods and in the registration applications of, among others, the innovative new drugs, the applicants may propose to conduct communication meetings with the CDE. The communication meetings can be classified into three types. Type I meetings are convened to address key safety issues in clinical trials of drugs and key technical issues in the research and development of breakthrough therapeutic drugs. Type II meetings are held during the key research and development periods of drugs, mainly including meetings before the IND, meetings upon the completion of Phase II trials and before the commencement of Phase III trials, meetings before submitting a marketing application for a new drug, and meetings for risk evaluation and control. Type III meetings refer to meetings not classified as Type I or Type II.

Sampling and Collecting Human Genetic Resources Filing

The Interim Administrative Measures on Human Genetic Resources (人類遺傳資源管理暫行辦法), promulgated by the Ministry of Science and Technology and the MOH on June 10, 1998, aimed at protecting and fair utilizing human genetic resources in the PRC. On July 2, 2015, the Ministry of Science and Technology issued the Service Guide for Administrative Licensing Items concerning Examination and Approval of Sampling, Collecting, Trading or Exporting Human Genetic Resources, or Taking Such Resources out of the PRC (人類遺傳資源採集、收集、買賣、出口、出境審批行政許可事項服務指南), or the Service Guide, which became effective on October 1, 2015. According to the Service Guide, the sampling, collection or research activities of human genetic resources by a foreign-invested sponsor fall within the scope of international cooperation, and the cooperating organization of China shall apply for approval of the China Human Genetic Resources Management Office through the online system. On October 26, 2017, the Ministry of Science and Technology promulgated the Circular on Optimizing the Administrative Examination and Approval of Human Genetic Resources (關於優化人類遺傳資源行政審批流程的通知), simplifying the approval of sampling and collecting human genetic resources for the purpose of listing a drug in the PRC.

The Regulations of the People's Republic of China on the Administration of Human Genetic Resources promulgated by the State Council on June 10, 2019 and implemented on July 1, 2019, further stipulates that in order to obtain marketing authorization for relevant drugs and medical devices in China, no approval is required in international clinical trial cooperation using China's human genetic resources at clinical institutions without export of human genetic resource materials. However, the two parties shall file the type, quantity and usage of the human genetic resource to be used with the administrative department of science and technology under the State Council before clinical trials.

Sample Manufacturing Practice

According to the Administrative Measures for Drug Registration, all facilities and techniques used in the manufacture of drug samples for clinical trial use in the PRC must conform to GMP guidelines as established by the NMPA.

International Multi-Center Clinical Trials Regulations and Acceptance of Overseas Clinical Trial Data

According to the International Multi-Center Clinical Trial Guidelines (Trial) (國際多中心藥物臨床試驗指南(試行)), or the Multi-Center Clinical Trial Guidelines, promulgated by the NMPA on January 30, 2015 and effective from March 1, 2015, international multi-center clinical trial applicants may simultaneously perform clinical trials in different centers using the same clinical trial protocol. Where the applicants plan to implement the International Multi-center clinical trials in the PRC, the applicants shall comply with relevant laws and regulations, such as the PRC Drug Administration Law, the Implementing Regulations of the PRC Drug Administration Law and the Administrative Measures for Drug Registration, execute the GCP, make reference to universal international principles such as the ICH-GCP, and comply with the laws and regulations of the countries involved in the International Multi-Center clinical trials. Where the applicants plan to use the data derived from the International Multi-Center clinical trials for approval of a BLA in the PRC, it shall involve at least two countries, including China, and shall satisfy the requirements for clinical trials set forth in the International Multi-Center Clinical Trial Guidelines (Trial) and Administrative Measures for Drug Registration.

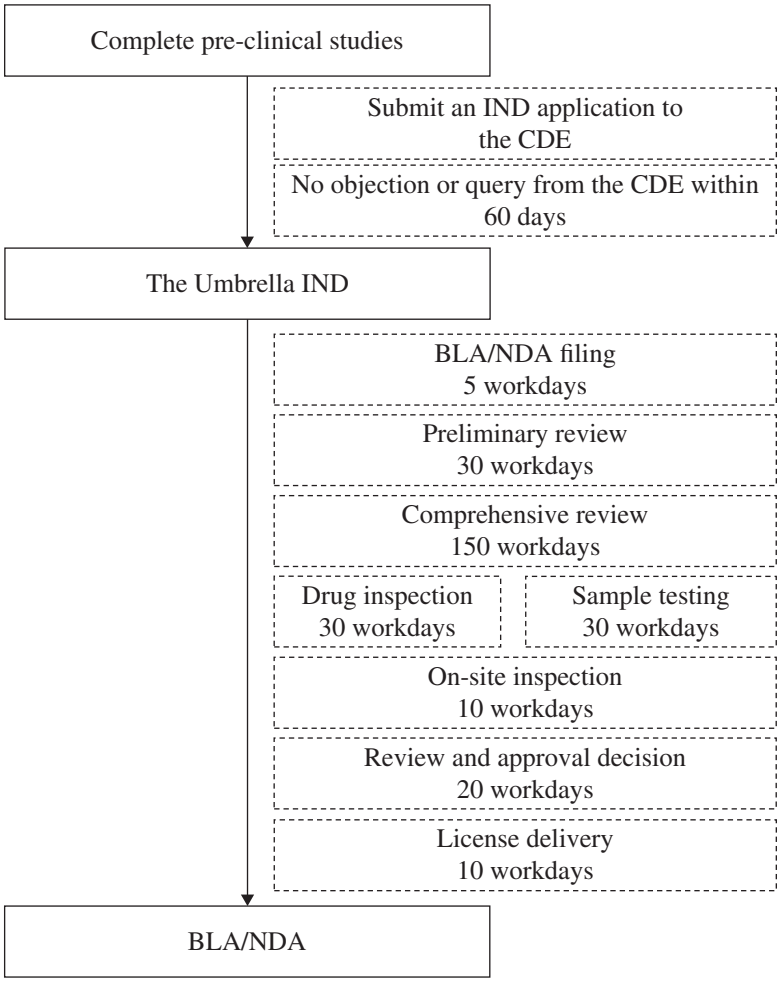
According to the Multi-Center Clinical Trial Guidelines, pivotal study refers to the clinical trial of the drug used for supporting the evaluation of the safety and effectiveness of the drug for marketing, which is usually the randomized blind controlled Phase III clinical trial. For details of the requirements of Phase III clinical trials, see "—Phases of Clinical Trials and the Communication with the CDE".

According to the Technical Guiding Principles for the Acceptance of Overseas Clinical Trial Data of Drugs (接受藥品境外臨床試驗數據的技術指導原則) promulgated by the NMPA on July 6, 2018, the basic principles for accepting overseas clinical trial data include: (1) applicants shall ensure the authenticity, integrity, accuracy and traceability of overseas clinical trial data; (2) the process of generating overseas clinical trial data shall comply with the relevant requirements of the Good Clinical Practice (GCP) of International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH); (3) applicants shall ensure the scientific design of overseas clinical trials, the compliance of clinical trial quality management system with the requirements, and the accuracy and integrity of statistical analysis of data; and (4) to ensure that the clinical trial design and statistical analysis of the data are scientific and reasonable, for the drugs with simultaneous R&D at home and abroad and forthcoming clinical trials in China, the applicants may, prior to implementing key clinical trials, contact the CDE to ensure the compliance of their design with the essential technical requirements for drug registration in China.

New Drug Application

According to the Administrative Measures for Drug Registration, drug registration applications include domestic new drug application, domestic generic drug application and imported drug application. Drugs are classified as chemical drugs, biological products and traditional Chinese medicine or natural drugs. When Phases I, II and III of clinical trials have been completed, the applicant may apply to the NMPA for approval of a new drug application. The NMPA then determines whether to approve the application according to the comprehensive evaluation opinion provided by the CDE of the NMPA.

According to the Opinions on Encouraging the Prioritized Evaluation and Approval for Drug Innovations, for new drugs which are developed for severe, life-threatening diseases currently lacking effective treatment and have great significance for meeting clinical needs, if, based on early-stage clinical trial data, the clinical benefits of such drugs can be reasonably predicted or decided and such drugs have distinctive advantages comparing with existing treatments, such new drugs may obtain a conditional approval for marketing before the completion of Phase III clinical trials undertaken to confirm its therapeutic effectiveness.



Registration of Biosimilar Drugs

Before 2015, there were lack of specific pathway and guidance for the registration, R&D and evaluation techniques of biosimilar drugs. Administrative Measures for Drug Registration only defines therapeutic biological products and prescribes that such drugs shall be registered in accordance with the new drug application procedures. Pursuant to these application procedures for new drugs, applicants are not required to conduct head-to-head clinical trials to test the bio-similarity of their drug candidates.

On February 28, 2015, NMPA promulgated the Announcement on Promulgating the Guiding Principles for the Research and Development and Evaluation Techniques concerning Biosimilar Drugs (關於發佈《生物類似藥研發與評價技術指導原則》的通告), or the 2015 Guiding Principles Announcement. The 2015 Guiding Principles Announcement clarifies that the registration procedures and R&D requirements of biosimilar.

The 2015 Guiding Principles Announcement does not set up new procedural requirements, nor provide a specific regulatory pathway for the registration of biosimilar drugs. Pursuant to the 2015 Guiding Principles Announcement, biosimilar drugs shall be registered according to the application procedures for new drugs. See "—New Drug Application" for details.

In addition, the 2015 Guiding Principles Announcement defines biosimilar drugs as therapeutic biological products similar to registered reference drugs in terms of quality, safety and efficacy. Depending on their nature and preparation method, biosimilar drugs shall be applied for registration under the corresponding categories (namely, Categories 2, 10 and 15) of therapeutic biological products listed in Appendix III to the Administrative Measures for Drug Registration. Applicants shall submit relevant application materials in accordance with the registration requirements for different categories of therapeutic biological products, respectively, as well as the 2015 Guiding Principles Announcement.

Furthermore, the 2015 Guiding Principles Announcement provides specific requirements for the R&D of biosimilar drugs. Under the 2015 Guiding Principles Announcement, applicants for registration of biosimilar drugs are required to prove the similarities between their drug candidates and the reference drugs through contrast experimental studies, so as to support the safety, efficacy and quality of such drugs. If the product is researched and developed pursuant to such requirements for biosimilar drugs, applicant shall make relevant statement in the Application Form for Drug Registration (《藥品註冊申請表》).

Special Examination and Fast Track Approval for Antineoplastic Drugs under Current Reform Frame

According to the Provisions on the Administration of Special Examination and Approval of Registration of New Drugs (新藥註冊特殊審批管理規定) promulgated by the NMPA on January 7, 2009, special examination and approval for new drugs registration applications applies when (1) the effective constituent of a drug extracted from plants, animals, minerals,

etc., as well as the preparations thereof, have never been marketed in China, and the material medicines and the preparations thereof are newly discovered, (2) the chemical raw materials for medicines as well as the preparations thereof and the biological product have not been approved for marketing, either in China or abroad, (3) new drugs with distinctive clinical treatment advantages for diseases such as AIDS, malignant tumor or other rare diseases or (4) new drugs for diseases that currently lacking effective treatment. Under the circumstances set out in (1) and (2), drug registration applicants may make special approval applications in submitting applications for clinical trials of new drugs; under the circumstances set out in (3) and (4), drug registration applicants may make special approval applications only in applying for production.

According to the Opinions on Reform of the Review & Approval System of Drugs and Medical Devices (關於改革藥品醫療器械審評審批制度的意見), a special review & approval system shall be adopted for innovative drugs to accelerate the review & approval of innovative drugs for prevention and treatment of AIDS, cancer, major infectious diseases, rare diseases and other diseases.

Announcement on Several Policies Pertaining to the Review & Approval of Drug Registration (關於藥品註冊審評審批若干政策的公告) further specifies that efforts shall be made to accelerate the review & approval of registration application for several categories of innovative drugs including those for prevention and treatment of cancer and other diseases. From December 1, 2015 onwards, applicants may apply to the CDE for accelerated review.

According to the Opinions on Encouraging the Priority Review & Approval for Drug Innovations (關於鼓勵藥品創新實行優先審評審批的意見), registration applications for cancer-combating drugs with noticeable clinical strength will be included in the scope of priority review & approval.

According to the Announcement on Matters Concerning the Optimization of Drug Registration Review & Approval (關於優化藥品註冊審評審批有關事宜的公告) jointly issued by the NMPA and the National Health Commission on May 23, 2018 and effective from the same date, the CDE will prioritize the allocation of resources for review, inspection, examination and approval of registration applications that have been included in the scope of priority review & approval so as to speed up review & approval.

Pilot Plan for the Marketing Authorization Holder System

According to the Reform Opinions, the pilot plan for the marketing authorization holder system, or the MAH system, shall be carried out.

Under the authorization of the NPCSC, the General Office of the State Council issued the Pilot Plan for the Drug Marketing Authorization Holder Mechanism (藥品上市許可持有人制度試點方案) on May 26, 2016, which provides a detailed pilot plan for the MAH system, for drugs in 10 provinces in China. Under the MAH system, domestic drug research and development institutions and individuals in the pilot regions are eligible to be holders of drug

registrations without having to become drug manufacturers. The marketing authorization holders may engage contract manufacturers for manufacturing, provided that the contract manufacturers are licensed and GMP-certified, and are also located within the pilot regions. Drugs that qualify for the MAH System are: (1) new drugs (including biological products approved as category I and VII drugs and biosimilars under the Administrative Measures for Drug Registration) approved after the implementation of the MAH System; (2) generic drugs approved as category III or IV drugs under the Reform Plan for Registration Category of Chemical Medicine (化學藥品註冊分類改革工作方案) issued by the NMPA on March 4, 2016; (3) previously approved generics that have passed equivalence assessments against original drugs; and (4) previously approved drugs whose licenses were held by drug manufacturers originally located within the pilot regions, but which have moved out of the pilot regions due to corporate mergers or other reasons.

The Circular on the Matters Relating to Promotion of the Pilot Program for the Drug Marketing Authorization Holder System (關於推進藥品上市許可持有人制度試點工作有關事項的通知), or the MAH Circular, promulgated by the NMPA on August 15, 2017, clarified the legal liability of the marketing authorization holder, who is responsible for managing the whole manufacturing and marketing chain and the whole life cycle of drugs and assumes the full legal liability for non-clinical drug study, clinical trials, manufacturing, marketing and distribution and adverse drug reaction monitoring. According to the MAH Circular, the marketing authorization holder shall submit a report of drug manufacturing, marketing, prescription, techniques, pharmacovigilance, quality control measures and other situations to the NMPA within 20 working days after the end of each year. The Decision of Extending the Period of Authorizing the State Council to Carry out the Pilot Plan for the Drug Marketing Authorization Holder Mechanism in Certain Places (關於延長授權國務院在部分地方開展藥品上市許可持有人制度試點期限的決定), promulgated by SCNPC on October 26, 2018, extended the term of MAH system to November 4, 2019.

The PRC Drug Administration Law was revised by the NPCSC on August 26, 2019 and will come into effect on December 1, 2019, provides that (1) the MAH system will be applicable throughout the country; (2) The legal representative and the key person-in-charge of a drug marketing authorization holder shall be fully responsible for the quality of drugs.

Monitoring Periods for New Drugs

According to the Implementing Regulations of the Drug Administration Law and the Administrative Measures for Drug Registration, the NMPA may, for the purpose of protecting public health, provide for an administrative monitoring period of not more than five years for new drugs approved to be manufactured, commencing from the date of approval, to continually monitor the safety of such new drugs. During the monitoring period of a new drug, no approval shall be granted to any other manufacturer to produce or import the said drug. The only exception is that if, prior to the commencement of the monitoring period, the NMPA has already approved any other IND of the same drug may proceed along drug registration application, review and approval procedures. Where regulations are conformed to, the NMPA shall approve the production or import of the same drug, and the monitoring of such drug produced by the domestic manufacturers should be conducted together with the drug already in the monitoring period.

Packaging of Pharmaceutical Products

According to the Measures for The Administration of Pharmaceutical Packaging (藥品包裝管理辦法) promulgated on February 12, 1988 and effective from September 1, 1988, pharmaceutical packaging must comply with national and professional standards. If there is no national or professional standard available, an applicant can formulate and implement its own standards after obtaining the approval of the provincial administration or bureau of standards. The applicant must reapply if it needs to change its own packaging standards. Drugs that have not been developed and approved for packaging standards must not be sold or marketed in the PRC (except for drugs for the military). According to the GCP Administration, the applicant shall be responsible for the proper packaging and labeling of drugs for clinical trials and in double-blind clinical trials, the test drug shall be consistent with the control drug or placebo in appearance, odor, packaging, labeling, and other features.

Healthcare System Reform

The PRC government recently promulgated several healthcare reform policies and regulations. On March 17, 2009, the Central Committee of the PRC Communist Party and the State Council jointly issued the Guidelines on Strengthening the Reform of Healthcare System (關於深化醫藥衛生體制改革的意見), On December 27, 2016, the State Council issued the Notice on the Issuance of the 13th Five-year Plan on Strengthening the Reform of Healthcare System (關於印發"十三五"深化醫藥衛生體制改革規劃的通知), On April 25, 2017, the General Office of the State Council issued the Main Tasks of Healthcare System Reform in 2017 (深化醫藥衛生體制改革2017年重點工作任務). Highlights of these healthcare reform policies and regulations include (1) establishing a basic healthcare system to cover both urban and rural residents and providing the Chinese people with safe, effective, convenient and affordable healthcare services, (2) improving the healthcare system through the reform and development of a graded hierarchical healthcare system, modern hospital management, basic medical insurance, drug supply support and comprehensive supervision, and (3) improving the efficiency and quality of the healthcare system to meet the various medical needs of the Chinese population.

Chronic Diseases Prevention and Treatment

According to the Guiding Opinion of the General Office of the State Council on Promoting the Construction of the Hierarchical Healthcare System (國務院辦公廳關於推進分級診療制度建設的指導意見), or the Hierarchical Healthcare System Opinion, issued by the General Office of the State Council on September 8, 2015, and the Notice on Promoting Pilot Work for Hierarchical Healthcare System (關於推進分級診療試點工作的通知) jointly promulgated by the NHFPC and the State Administration of Traditional Chinese Medicine on August 19, 2016, the hierarchical healthcare system is expected to be gradually improved. The Hierarchical Healthcare System Opinion further clarified that several chronic diseases, including hypertension, diabetes, cancer and cardiovascular and cerebrovascular diseases, are pilot diseases under the hierarchical healthcare system. Primary health institutions, rehabilitation hospitals, and nursing institutions can provide treatments, rehabilitation and nursing services to patients with chronic diseases, patients in rehabilitation, elderly patients and advanced tumor patients who have clear diagnosis and stable disease conditions.

On January 22, 2017, the General Office of the State Council promulgated the Mid and Long-Term Plan for Chronic Disease Prevention and Treatment in China (2017-2025) (中國防治慢性病中長期規劃(2017-2025年)), or the Chronic Disease Plan. One of its objectives is to raise up the overall 5-year survival rate in cancer patients by 5% by 2020 and 10% by 2025. It also points out that the hierarchical healthcare system of chronic diseases, such as tumor, shall be promoted. The social participation in regional medical services, as well as social investments in the field of chronic disease prevention and treatment is also encouraged.

PRC Coverage and Reimbursement

Coverage of the National Medical Insurance Program

The national medical insurance program was first adopted according to the Decision of the State Council on the Establishment of the Urban Employee Basic Medical Insurance Program (國務院關於建立城鎮職工基本醫療保險制度的決定) issued by the State Council on December 14, 1998, under which all employers in urban cities are required to enroll their employees in the basic medical insurance program and the insurance premium is jointly contributed by the employers and employees. On July 10, 2007, the State Council issued the Guiding Opinions of the State Council about the Pilot Urban Resident Basic Medical Insurance (國務院關於開展城鎮居民基本醫療保險試點的指導意見), further enlarged the coverage of the basic medical insurance program, under which urban residents of the pilot district, rather than urban employees, may voluntarily join Urban Resident Basic Medical Insurance. In addition, on January 3, 2016, the Opinions on Integrating the Basic Medical Insurance Systems for Urban and Rural Residents (國務院關於整合城鄉居民基本醫療保險制度的意見) issued by the State Council required the integration of the urban resident basic medical insurance and the new rural cooperative medical care system and the establishment of a unified basic medical insurance system, which will cover all urban and rural residents other than rural migrant workers and persons in flexible employment arrangements who participate in the basic medical insurance for urban employees.

Medical Insurance Catalogue

Program participants are eligible for full or partial reimbursement of the cost of medicines included in the medical insurance catalogue. The Notice Regarding the Tentative Measures for the Administration of the Scope of Basic Medical Insurance Coverage for Pharmaceutical Products for Urban Employee (關於印發城鎮職工基本醫療保險用藥範圍管理暫行辦法的通知), or the Medical Insurance Coverage Notice, jointly issued on May 12, 1999 by several authorities including, among others, the Ministry of Labor and Social Security and the Ministry of Finance, provides that a pharmaceutical product listed in the medical insurance catalogue must be clinically necessary, safe, effective, reasonably priced, easy to use, available in sufficient quantity, and must meet the following requirements: (1) be set forth in the pharmacopoeia of the PRC, (2) satisfy the standards promulgated by the NMPA, and (3) be approved by the NMPA for imported pharmaceutical products.

The National Drug Catalog for Basic Medical Insurance, Work-related Injury Insurance and Maternity Insurance (國家基本醫療保險、工傷保險和生育保險藥品目錄), or the NRDL, sets forth the payment standard for pharmaceutical products under the basic medical insurance, work-related injury insurance and maternity insurance funds. The MOHRSS (According to the above institutional reform, the functions with respect to change the NRDL have been transferred to the PRC National Health Insurance Bureau), together with other government authorities, has the power to determine which medicines are listed in the NRDL. Medicines listed in the NRDL are divided into two parts, List A and List B. List A drugs are widely used clinical treatments with good efficacy and lower prices compared to similar drugs, while List B drugs are clinical treatments with good efficacy and slightly higher prices compared to List A drugs.

On July 13, 2017, the MOHRSS announced that the 2017 NRDL would be expanded to include an additional 36 drugs classified as List B medicines, 18 of which are anti-cancer drugs. On September 30, 2018, the PRC National Health Insurance Bureau announced that another 17 anti-cancer drugs were included into the 2017 NRDL classified as List B Medicines. Since 2017, the NRDL has reflected an emphasis on drugs that treat cancer.

According to the Medical Insurance Coverage Notice, a PRDL must be made by the labor administration departments of the provincial governments in the PRC. Provincial evaluation institutions and expert groups select the drugs to be listed in the PRDL. Provincial governments are required to include all List A drugs listed in the NRDL in their PRDL, but have discretion to adjust upwards or downwards by no more than 15% the number of List B drugs listed in the NRDL to be listed in the PRDL based on local economic levels, medical demands, and medication practices.

According to the Medical Insurance Coverage Notice, patients purchasing List A drugs listed in the NRDL are entitled to reimbursement of the entire amount of the purchase price through the basic medical insurance program. Patients purchasing List B drugs listed in the NRDL are required to pay a certain percentage of the purchase price and obtain reimbursement for the remainder of the purchase price through the basic medical insurance program.

The NRDL must be adjusted every two years in principle, and the PRDL must be adjusted based on the adjustment of the NRDL. The PRDL can only be adjusted according to the respective adjustment of the NRDL, and all adjustments to the List A drugs in the NRDL are required to be made in the PRDL. The NRDL is permitted to be expanded for new drugs once every year, while provincial governments are not permitted to expand the PRDL for new drugs.

The Opinions on Promoting Drug Pricing Reform (推進藥品價格改革的意見), which was promulgated by the NDRC, the NHFPC, NMPA, Ministry of Commerce and certain other departments on May 4, 2015, and came into effect on June 1, 2015, set forth that from June 1, 2015, except for narcotic drugs and Class I psychotropic drugs, the restrictions on the prices of the drugs that were subject to government pricing will be cancelled. The medical insurance regulatory authority shall, along with other competent departments, draw up provisions in relation to the standards, procedures, basis and methods of the payment of drugs paid by

medical insurance funds. The prices of patent drugs and exclusively produced drugs are set through transparent and public negotiation among multiple parties. The prices for blood products not listed in the Medical Insurance Drugs List, immunity and prevention drugs that are purchased by the government in a centralized manner, and AIDS antiviral drugs and contraceptives provided by the government for free, shall be set through tendering purchase or negotiation. Except as otherwise mentioned above, the prices for other drugs may be determined by manufacturers and operators on their own on the basis of production or operation costs and market supply and demand. In addition, the 2017 NRDL proposed to explore the development of a negotiation mechanism for drugs to be listed in the NDRL. The MOHRSS will, in accordance with relevant criteria, negotiate for the drugs proposed to be negotiated as determined by experts upon review. Those eligible drugs will be included in the payment scope of the medical insurance fund.

According to the Opinions on Deepening the Reform of the Evaluation and Approval System and Inspiring Innovation of Drugs and Medical Devices, to support the clinical application of new drugs, (1) the dynamic adjustment mechanism applicable to the catalogue of drugs by medical insurance will be improved, (2) the establishment of a negotiation mechanism regarding payment standards for drugs covered by medical insurance will be explored, (3) new drugs will be promptly incorporated according to applicable provisions into the payment scope covered by basic medical insurance, and (4) research and development of new drugs will be supported.

Intellectual Property Rights

In terms of international conventions, China has entered into (including but not limited to) the Agreement on Trade-Related Aspects of Intellectual Property Rights (與貿易有關的知識產權協定), the Paris Convention for the Protection of Industrial Property (保護工業產權巴黎公約), the Madrid Agreement Concerning the International Registration of Marks (商標國際註冊馬德里協定) and the Patent Cooperation Treaty (專利合作協定).

Patents

According to the Patent Law of the PRC (中華人民共和國專利法) promulgated by the SCNPC on March 12, 1984, as amended on September 4, 1992, August 25, 2000 and December 27, 2008, and effective from October 1, 2009 and the Implementation Rules of the Patent Law of the PRC (中華人民共和國專利法實施細則), promulgated by the State Council on June 15, 2001 and as amended on December 28, 2002 and January 9, 2010, there are three types of patents in the PRC: invention patents, utility model patents and design patents. The protection period is 20 years for an invention patent and 10 years for a utility model patent and a design patent, commencing from their respective application dates. Any individual or entity that utilizes a patent or conducts any other activity in infringement of a patent without prior authorization of the patent holder shall pay compensation to the patent holder and is subject to a fine imposed by relevant administrative authorities and, if constituting a crime, shall be held criminally liable in accordance with the law. According to the PRC Patent Law, for public health purposes, the State Intellectual Property Office of the PRC may grant a compulsory

license for manufacturing patented drugs and exporting them to countries or regions covered under relevant international treaties to which PRC has acceded. In addition, according to the Patent Law, any organization or individual that applies for a patent in a foreign country for an invention or utility model patent established in China is required to report to the State Intellectual Property Office for confidentiality examination.

Trade Secrets

According to the PRC Anti-Unfair Competition Law (中華人民共和國反不正當競爭法), promulgated by the SCNPC in September 1993, as amended in November 4, 2017 and April 23, 2019 respectively, the term "trade secrets" refers to technical and business information that is unknown to the public, has utility, may create business interests or profits for its legal owners or holders, and is maintained as a secret by its legal owners or holders. Under the PRC Anti-Unfair Competition Law, business persons are prohibited from infringing others' trade secrets by: (1) obtaining the trade secrets from the legal owners or holders by any unfair methods such as theft, bribery, fraud, coercion, electronic intrusion, or any other illicit means; (2) disclosing, using or permitting others to use the trade secrets obtained illegally under item (1) above; or (3) disclosing, using or permitting others to use the trade secrets, in violation of any contractual agreements or any requirements of the legal owners or holders to keep such trade secrets in confidence. If a third party knows or should have known of the above-mentioned illegal conduct but nevertheless obtains, uses or discloses trade secrets of others, the third party may be deemed to have committed a misappropriation of the others' trade secrets. The parties whose trade secrets are being misappropriated may petition for administrative corrections, and regulatory authorities may stop any illegal activities and fine infringing parties.

Trademarks

According to the Trademark Law of the PRC (中華人民共和國商標法), promulgated by the SCNPC on August 23, 1982, amended on February 22, 1993, October 27, 2001 and August 30, 2013 and April 23, 2019, and the latest amendment became effective from November 1, 2019, the period of validity for a registered trademark is 10 years, commencing from the date of registration. Upon expiry of the period of validity, the registrant shall go through the formalities for renewal within twelve months prior to the date of expiry, if intending to continue to use the trademark. Where the registrant fails to do so, a grace period of six months may be granted. The period of validity for each renewal of registration is 10 years, commencing from the day immediately after the expiry of the preceding period of validity for the trademark. In the absence of a renewal upon expiry, the registered trademark shall be canceled. Industrial and commercial administrative authorities have the authority to investigate any behavior in infringement of the exclusive right under a registered trademark in accordance with the law. In case of a suspected criminal offense, the case shall be timely referred to a judicial authority and decided according to law.

Domain Names

Domain names are protected under the Administrative Measures on the Internet Domain Names (互聯網域名管理辦法) issued by the Ministry of Industry and Information Technology, or the MIIT, on August 24, 2017 and effective from November 1, 2017, and the Implementing Rules on Registration of Domain Names (中國互聯網絡信息中心域名註冊實施細則) issued by China Internet Network Information Center on May 28, 2012, which became effective on May 29, 2012. The MIIT is the main regulatory body responsible for the administration of PRC internet domain names. Domain name registrations are handled through domain name service agencies established under the relevant regulations, and the applicants become domain name holders upon successful registration.

Product Liability

The Product Quality Law of the PRC (中華人民共和國產品質量法) promulgated by the SCNPC on February 22, 1993 and amended on July 8, 2000, August 27, 2009 and December 29, 2018, is the principal governing law relating to the supervision and administration of product quality, which clarified liabilities of the manufactures and sellers. Manufactures shall not be liable when they are able to prove that: (1) the product has never been circulated; (2) the defects causing injuries or damage did not exist at the time when the product was circulated; or (3) the science and technology at the time when the product was circulated were at a level incapable of detecting the defects. A seller shall pay compensation if it fails to indicate neither the manufacturer nor the supplier of the defective product. A person who is injured or whose property is damaged by the defects in the product may claim for compensation from the manufacturer or the seller.

According to the Tort Liability Law of the PRC (中華人民共和國侵權責任法), promulgated by the SCNPC on December 26, 2009 and effective from July 1, 2010, manufacturers shall assume tort liability where the defects in relevant products cause damage to others. Sellers shall assume tort liability where the defects in relevant products causing damage to others are attributable to the sellers. The aggrieved party may claim for compensation from the manufacturer or the seller of the relevant product in which the defects have caused damage.

Environmental Protection

According to the Environmental Protection Law of the PRC (中華人民共和國環境保護法), promulgated by the SCNPC on December 26, 1989 and amended on April 24, 2014, the Environmental Impact Assessment Law of the PRC (中華人民共和國環境影響評價法), promulgated by the SCNPC on October 28, 2002 and amended on July 2, 2016 and December 29, 2018 respectively, the Administrative Regulations on the Environmental Protection of Construction Project (建設項目環境保護管理條例), promulgated by the State Council on November 29, 1998 and amended on July 16, 2017, and other relevant environmental laws and regulations, enterprises which plan to construct projects shall provide the assessment reports, assessment form, or registration form on the environmental impact of such projects with

relevant environmental protection administrative authority for approval or filing. The composition of assessment reports and assessment forms shall be undertaken by institutions qualified for assessment of environmental impact engaged by enterprises planning to construct projects.

According to the Law of the PRC on the Prevention and Control of Water Pollution (中華人民共和國水污染防治法) promulgated by the SCNPC on May 11, 1984 and amended on May 15, 1996, February 28, 2008 and June 27, 2017, and effective from January 1, 2018, the Law of the PRC on the Prevention and Control of Atmospheric Pollution (中華人民共和國大氣污染防治法) promulgated by the SCNPC on September 5, 1987 and amended on August 29, 1995, April 29, 2000, August 29, 2015 and October 26, 2018 respectively, the Law of the PRC on the Prevention and Control of Pollution from Environmental Noise (中華人民共和國環境噪聲污染防治法) promulgated by the SCNPC on October 29, 1996 and amended on December 29, 2018, and the Law of the PRC on the Prevention and Control of Environmental Pollution of Solid Waste (中華人民共和國固體廢物污染環境防治法), promulgated by the SCNPC on October 30, 1995 and amended on December 29, 2004, June 29, 2013, April 24, 2015 and November 7, 2016, all the enterprises that may cause environmental pollution in the course of their production and business operation shall introduce environmental protection measures in their plants and establish a reliable system for environmental protection.

Foreign Exchange Control

According to the PRC Regulation for the Foreign Exchange (中華人民共和國外匯管理條例), or the Foreign Exchange Regulations promulgated by the PRC State Council on January 29, 1996, which was amended on January 14, 1997 and August 5, 2008, and the Regulation on the Administration of the Foreign Exchange Settlement, Sales and Payment (結匯、售匯及付匯管理規定), or the Settlement Regulations promulgated by the People's Bank of China on June 20, 1996 and effective from July 1, 1996, foreign exchanges required for distribution of profits and payment of dividends may be purchased from designated foreign exchange banks in the PRC upon presentation of a board resolution authorizing distribution of profits or payment of dividends.

According to the Circular of SAFE on Further Improving and Adjusting the Foreign Exchange Policies on Direct Investment (國家外匯管理局關於進一步改進和調整直接投資外匯管理政策的通知) and its appendix, the Operating Rules for Foreign Exchange Issues with Regard to Direct Investment under Capital Account (資本項目直接投資外匯業務操作規程), promulgated on November 19, 2012 and amended on May 4, 2015 by the State Administration of Exchange Control, or the SAFE, (1) the opening of and payment into foreign exchange accounts under direct investment accounts are no longer subject to approval by the SAFE; (2) reinvestment with legal income of foreign investors in China is no longer subject to approval by SAFE; (3) the procedures for capital verification and confirmation that foreign-funded enterprises need to go through are simplified; (4) purchase and external payment of foreign exchange under direct investment accounts are no longer subject to approval by SAFE; (5) domestic transfer of foreign exchange under direct investment account is no longer subject to approval by SAFE; and (6) the administration over the conversion of foreign exchange capital

of foreign-invested enterprises is improved. Later, on February 13, 2015, the SAFE issued the Circular on Further Simplifying and Improving Foreign Exchange Administration Policies in Respect of Direct Investment (關於進一步簡化和改進直接投資外匯管理政策的通知), effective from June 1, 2015, which prescribed that the bank instead of SAFE can directly handle the foreign exchange registration and approval under foreign direct investment while SAFE and its branches indirectly supervise the foreign exchange registration and approval under foreign direct investment through the bank.

The Provisions on the Administration of Foreign Exchange in Foreign Direct Investments by Foreign Investors (外國投資者境內直接投資外匯管理規定), or the FDI Provisions, which were promulgated by the SAFE on May 11, 2013 and became effective on May 13, 2013, and as amended on October 10, 2018, regulate and clarify the administration over foreign exchange administration in foreign direct investments.

According to the Circular on the Reform of the Management Method for the Settlement of Foreign Exchange Capital of Foreign-invested Enterprises (國家外匯管理局關於改革外商投資企業外匯資本金結匯管理方式的通知) promulgated by the SAFE on March 30, 2015 and effective from June 1, 2015, and the Circular on the Reform and Standardization of the Management Policy of the Settlement of Capital Projects (國家外匯管理局關於改革和規範資本項目結匯管理政策的通知) promulgated by the SAFE on June 9, 2016, the settlement of foreign exchange by foreign invested enterprises shall be governed by the policy of foreign exchange settlement on a discretionary basis. However, the settlement of foreign exchange shall only be used for its own operation purposes within the business scope of the foreign invested enterprises and following the principles of authenticity.

The SAFE promulgated the Circular 37 on July 4, 2014. The Circular 37 requires PRC residents to register with the local branches of SAFE in connection with their direct establishment or indirect control of an offshore entity, for the purpose of overseas investment and financing, with such PRC residents' legally owned assets or equity interests in domestic enterprises or offshore assets or interests. Failure to comply with the SAFE registration requirements could result in liability under PRC law for evasion of foreign exchange controls. The Circular on Further Simplifying and Improving Foreign Exchange Administration Policies in Respect of Direct Investment provides that the bank instead of SAFE can directly handle the initial foreign exchange registration and amendment registration under Circular 37.

Labor and Social Insurance

According to the PRC Labor Law (中華人民共和國勞動法), which was promulgated by the SCNPC on July 5, 1994 and effective from January 1, 1995, and amended on August 27, 2009 and December 29, 2018 respectively, the PRC Labor Contract Law (中華人民共和國勞動合同法), which was promulgated by the SCNPC on June 29, 2007 and effective from January 1, 2008, and amended on December 28, 2012 and effective from July 1, 2013, and the Implementing Regulations of the Employment Contracts Law of the PRC (中華人民共和國勞動合同法實施條例), which was promulgated by the State Council on September 18, 2008, labor contracts in written form shall be executed to establish labor relationships between employers

and employees. In addition, wages cannot be lower than local minimum wage. The employers must establish a system for labor safety and sanitation, strictly abide by State rules and standards, provide education regarding labor safety and sanitation to its employees, provide employees with labor safety and sanitation conditions and necessary protection materials in compliance with State rules, and carry out regular health examinations for employees engaged in work involving occupational hazards.

According to the Social Insurance Law of PRC (中華人民共和國社會保險法), which was promulgated by the SCNPC on October 28, 2010 and effective from July 1, 2011, and amended on December 29, 2018, the Interim Regulations on the Collection and Payment of Social Security Funds (社會保險費徵繳暫行條例), which was promulgated by the State Council on January 22, 1999 and amended on March 24, 2019, and the Regulations on the Administration of Housing Provident Funds (住房公積金管理條例), which was promulgated by the State Council on April 3, 1999 and amended on March 24, 2002 and March 24, 2019, employers are required to contribute, on behalf of their employees, to a number of social security funds, including funds for basic pension insurance, unemployment insurance, basic medical insurance, occupational injury insurance, maternity insurance and to housing provident funds. Any employer who fails to contribute may be fined and ordered to make good the deficit within a stipulated time limit.

Dividend Distribution

According to the PRC Company Law, the PRC Foreign-Owned Enterprise Law and the Implementing Rules for the PRC Foreign-Owned Enterprise Law, foreign-invested enterprises in the PRC may pay dividends only out of their accumulated profits as determined in accordance with PRC accounting standards and regulations. A foreign-invested enterprise is required to set aside at least 10% of its respective accumulated profits each year to fund certain reserve funds, until the accumulative amount of such fund reaches 50% of its registered capital. These wholly foreign-owned companies may also allocate a portion of their after-tax profits based on PRC accounting standards to staff welfare and bonus funds. Amounts allocated to these reserve funds and staff welfare and bonus funds reduce the amount distributable as cash dividends. Upon approval of the competent governmental authorities, foreign investors may utilize RMB dividends to invest or re-invest in enterprises established in China.

According to the Notice on Improving the Check of Authenticity and Compliance to Further Promote Foreign Exchange Control (國家外匯管理局關於進一步推進外匯管理改革完善真實合規性審核的通知) promulgated by the SAFE on January 26, 2017, (1) under the principle of genuine transaction, banks shall check board resolutions regarding profit distribution, the original version of tax filing records and audited financial statements; and (2) domestic entities shall hold income to account for previous years' losses before remitting the profits. Moreover, domestic entities shall make detailed explanations of sources of capital and utilization arrangements, and provide board resolutions, contracts and other proof when completing the registration procedures in connection with an outbound investment.

Employee Stock Incentive Plan

On February 15, 2012, the SAFE promulgated the Notices on Issues Concerning the Foreign Exchange Administration for Domestic Individuals Participating in Stock Incentive Plans of Overseas Publicly Listed Companies (國家外匯管理局關於境內個人參與境外上市公司股權激勵計劃外匯管理有關問題的通知), or the Stock Option Rules, which prescribed that PRC citizens or non-PRC citizens residing in China for a continuous period of no less than one year (except for foreign diplomatic personnel in China and representatives of international organizations in China) who participate in any stock incentive plan of an overseas publicly listed company shall, through the domestic company to which the said company is affiliated, collectively entrust a domestic agency (may be the Chinese affiliate of the overseas publicly listed company which participates in stock incentive plan, or other domestic institutions qualified for asset trust business lawfully designated by such company) to handle foreign exchange registration, and entrust an overseas institution to handle issues like exercise of options, purchase and sale of corresponding stocks or equity, and transfer of corresponding funds. In addition, the domestic agency is required to amend the SAFE registration with respect to the stock incentive plan if there is any material change to the stock incentive plan. Moreover, the Circular 37 provides that PRC residents who participate in a share incentive plan of an overseas unlisted special purpose company may register with local branches of SAFE before exercising rights.

Enterprise Income Tax

According to the EIT Law promulgated by the National People's Congress on March 16, 2007, which became effective on January 1, 2008 and was amended on February 24, 2017 and December 29, 2018, and the Implementation Rules of the Enterprise Income Tax Law of the PRC (中華人民共和國企業所得税法實施條例) promulgated by the State Council on December 6, 2007, which became effective on January 1, 2008, other than a few exceptions, the income tax rate for both domestic enterprises and foreign-invested enterprises is 25%. Enterprises are classified as either "resident enterprises" or "non-resident enterprises". Besides enterprises established within the PRC, enterprises established outside China whose "de facto management bodies" are located in China are considered "resident enterprises" and subject to the uniform 25% enterprise income tax rate for their global income. A non-resident enterprise refers to an entity established under foreign law whose "de facto management bodies" are not within the PRC but which have an establishment or place of business in the PRC, or which do not have an establishment or place of business in the PRC but have income sourced within the PRC. An income tax rate of 10% will normally be applicable to dividends declared to non-PRC resident enterprise investors that do not have an establishment or place of business in the PRC, or that have such establishment or place of business but the relevant income is not effectively connected with the establishment or place of business, to the extent such dividends are derived from sources within the PRC.

According to an Arrangement Between the Mainland of China and the Hong Kong Special Administrative Region for the Avoidance of Double Taxation and Prevention of Fiscal Evasion with Respect to Taxes on Income (內地和香港特別行政區關於對所得避免雙重徵税和防止偷

漏税的安排), or the Double Tax Avoidance Arrangement, and other applicable PRC laws, if a Hong Kong resident enterprise is determined by the competent PRC tax authority to have satisfied the relevant conditions and requirements under such Double Tax Avoidance Arrangement and other applicable laws, the 10% withholding tax on the dividends the Hong Kong resident enterprise receives from a PRC resident enterprise may be reduced to 5%. However, based on the Circular on Certain Issues with Respect to the Enforcement of Dividend Provisions in Tax Treaties (關於執行税收協定股息條款有關問題的通知) issued on February 20, 2009 by the SAT, if the relevant PRC tax authorities determine, in their discretion, that a company benefits from such reduced income tax rate due to a structure or arrangement that is primarily tax-driven, such PRC tax authorities may adjust the preferential tax treatment; and based on the Announcement on Certain Issues with Respect to the "Beneficial Owner" in Tax Treaties (國家税務總局關於税收協定中"受益所有人"有關問題的公告) issued by the SAT on February 3, 2018 and effective from April 1, 2018, if an applicant's business activities do not constitute substantive business activities, it could result in the negative determination of the applicant's status as a "beneficial owner", and consequently, the applicant could be precluded from enjoying the above-mentioned reduced income tax rate of 5% under the Double Tax Avoidance Arrangement.

LAWS AND REGULATIONS IN THE UNITED STATES

U.S. Government Regulation of Drug and Biological Products

In the United States, the FDA regulates drugs under the FDCA, and its implementing regulations and biologics under the FDCA and the Public Health Service Act, or PHSA, and their implementing regulations. Both drugs and biologics also are subject to other federal, state and local statutes and regulations, such as those related to competition. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, and local statutes and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or following approval may subject an applicant to administrative actions or judicial sanctions. These actions and sanctions could include, among other actions, the FDA's refusal to approve pending applications, withdrawal of an approval, license revocation, a clinical hold, untitled or warning letters, voluntary or mandatory product recalls or market withdrawals, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement and civil or criminal fines or penalties. Any agency or judicial enforcement action could have a material adverse effect on our business, the market acceptance of our products and our reputation.

Once a product candidate is identified for development, it enters pre-clinical testing, which includes laboratory evaluations of product chemistry, toxicity, formulation and stability, as well as animal studies. Pre-clinical testing is conducted in accordance with FDA's Good Laboratory Practice, or GLP, regulations. A sponsor of an IND must submit the results of the pre-clinical tests, manufacturing information, analytical data, the clinical trial protocol, and any available clinical data or literature to the FDA. The IND automatically becomes effective

30 days after receipt by the FDA, unless the FDA raises concerns or questions and places the trial on a clinical hold within that 30-day time period. FDA may also impose clinical holds or partial clinical holds at any time during clinical trials due to safety concerns or noncompliance.

All clinical trials, which involve the administration of the investigational product to humans, must be conducted under the supervision of one or more qualified investigators in accordance with Good Clinical Practice, or GCP, regulations, including the requirement that all research subjects provide informed consent in writing before their participation in any clinical trial. Further, an Institutional Review Board, or IRB, must review and approve the plan for any clinical trial before it commences at any institution, and the IRB must conduct continuing review and reapprove the study at least annually. Each new clinical protocol and any amendments to the protocol must be submitted for FDA review, and to the IRBs for approval. An IRB can suspend or terminate approval of a clinical trial at its institution if the trial is not being conducted in accordance with the IRB's requirements or if the product has been associated with unexpected serious harm to subjects.

Clinical trials generally are conducted in three sequential phases, known as Phase I, Phase II and Phase III, and may overlap.

- Phase I clinical trials generally involve a small number of healthy volunteers or disease-affected patients who are initially exposed to a single dose and then multiple doses of the product candidate. The primary purpose of these clinical trials is to assess the metabolism, pharmacologic action, side effect tolerability and safety of the product candidate.

- Phase II clinical trials involve studies in disease-affected patients to evaluate proof of concept and/or determine the dose required to produce the desired benefits. At the same time, safety and further PK and PD information is collected, possible adverse effects and safety risks are identified and a preliminary evaluation of efficacy is conducted.

- Phase III clinical trials generally involve a large number of patients at multiple sites and are designed to provide the data necessary to demonstrate the effectiveness of the product for its intended use, its safety in use and to establish the overall benefit/risk relationship of the product and provide an adequate basis for product labeling.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA. Safety reports must be submitted to the FDA and the investigators 15 calendar days after the trial sponsor determines that the information qualifies for reporting. The sponsor also must notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information. Sponsors of clinical trials of FDA-regulated products, including drugs, are required to register and disclose certain clinical trial information, which is publicly available at www.clinicaltrials.gov.

Concurrent with clinical trials, companies usually complete additional animal studies and must also finalize a process for manufacturing the product in commercial quantities in accordance with cGMP, requirements. The process of obtaining regulatory approvals and compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources. Failure to comply with the applicable U.S. requirements may subject an applicant to administrative or judicial sanctions.

U.S. Review and Approval Processes

The results of product development, pre-clinical studies and clinical trials, along with descriptions of the manufacturing process, analytical tests conducted on the product, proposed labeling and other relevant information, are submitted to the FDA as part of a BLA. Unless deferred or waived, BLAs, or supplements must contain data adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The submission of a BLA is subject to the payment of a substantial user fee and an annual prescription drug product program fee.

Within 60 days of its receipt, the FDA reviews the BLA to ensure that it is sufficiently complete for substantive review before it accepts the BLA for filing. After accepting the BLA filing, the FDA begins an in-depth substantive review to determine, among other things, whether a product is safe and effective for its intended use. The FDA also evaluates whether the product's manufacturing is cGMP-compliant to assure the product's identity, strength, quality and purity. Before approving the BLA, the FDA typically will inspect whether the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. The FDA may refer the BLA to an advisory committee, a panel of experts, for review whether the application should be approved and under what conditions and considers such recommendations when making decisions.

The FDA may refuse to approve the BLA if the applicable regulatory criteria are not satisfied or may require additional clinical data or other data and information. The FDA will issue a complete response letter describing all of the specific deficiencies that the FDA identified in the BLA that must be satisfactorily addressed before it can be approved. The deficiencies identified may be minor, for example, requiring labeling changes, or major, for example, requiring additional clinical trials. Additionally, the complete response letter may include recommended actions that the applicant might take to place the application in a condition for approval. The applicant may either resubmit the BLA, addressing all of the deficiencies identified in the letter, or withdraw the application or request an opportunity for a hearing.

The regulatory approval may be limited to specific diseases and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling. In addition, the FDA may require post-approval studies, including phase IV clinical trials, to further assess a product's safety and effectiveness after BLA approval and may require testing and surveillance programs to monitor the safety of approved products that have been commercialized.

Expedited Development and Review Programs

Accelerated Approval

Under FDA's accelerated approval regulations, the FDA may approve a drug or biologic candidate for a serious or life-threatening illness that provides meaningful therapeutic benefit to patients over existing treatments and demonstrates an effect on either a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, or IMM, that is reasonably likely to predict an effect on IMM or other clinical benefit, taking into account the severity, rarity, or prevalence of the disease or condition and the availability or lack of alternative treatments. A product candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of post-approval clinical trial to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or to confirm a clinical benefit during post-marketing studies, will allow the FDA to withdraw the product from the market on an expedited basis. All promotional materials for product candidates approved under accelerated regulations are subject to prior review by the FDA.

Breakthrough Designation

Another program available for sponsors is the breakthrough therapy designation. A drug or biologic may be eligible for designation as a breakthrough therapy if the product is intended, alone or in combination with one or more other drugs or biologics, to treat a serious or life-threatening condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over currently approved therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. A sponsor may request that a product be designated as a breakthrough therapy concurrently with, or at any time after, the submission of an IND, and the FDA must determine if the candidate qualifies for such designation within 60 days of receipt of the request. If so designated, the FDA shall act to expedite the development and review of the product's marketing application, including by meeting with the sponsor throughout the product's development, providing timely advice to the sponsor to ensure that the development program to gather pre-clinical and clinical data is as efficient as practicable.

Orphan Drugs

Under the Orphan Drug Act, the FDA may grant orphan drug designation to drugs or biologic candidates intended to treat a rare disease or condition generally affecting fewer than 200,000 individuals in the U.S. The first applicant to receive FDA approval for the disease or indication for which it has orphan drug designation is entitled to a seven-year exclusive marketing period. During the exclusivity period, the FDA may not approve any other applications to market the same product for the same disease or condition except in limited circumstance.

Post-Marketing Requirements

Following approval of a new product, the manufacturer and the approved product are subject to continuing regulation by the FDA, including, among other things, monitoring and record-keeping activities, reporting of adverse experiences, complying with promotion and advertising requirements, which include restrictions on promoting products for unapproved uses or patient populations (known as "off-label use") and limitations on industry-sponsored scientific and educational activities. Although physicians may prescribe legally available products for off-label uses, manufacturers may not market or promote such uses. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability, including investigation by federal and state authorities. Prescription drug promotional materials must be submitted to the FDA in conjunction with their first use or first publication. Further, if there are any modifications to the drug or biologic, including changes in indications, labeling or manufacturing processes or facilities, the applicant may be required to submit and obtain FDA approval of a new BLA or BLA supplement, which may require the development of additional data or pre-clinical studies and clinical trials.

The FDA may also place other conditions on approvals including the requirement for a REMS, to assure the safe use of the product. If the FDA concludes a REMS is needed, the sponsor of the BLA must submit a proposed REMS. The FDA will not approve the BLA without an approved REMS, if required. A REMS could include medication guides, physician communication plans or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. Any of these limitations on approval or marketing could restrict the commercial promotion, distribution, prescription or dispensing of products. Product approvals may be withdrawn for non-compliance with regulatory standards or if problems occur following initial marketing.

FDA regulations require that products be manufactured in specific approved facilities and in accordance with cGMP regulations. We rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of our products in accordance with cGMP regulations. These manufacturers must comply with cGMP regulations that require, among other things, quality control and quality assurance, the maintenance of records and documentation and the obligation to investigate and correct any deviations from cGMP.

Manufacturers and other entities involved in the manufacture and distribution of approved drugs or biologics are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP requirements and other laws. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain cGMP compliance. The discovery of violative conditions, including failure to conform to cGMP regulations, could result in enforcement actions, and the discovery of problems with a product after approval may result in restrictions on a product, manufacturer or holder of an approved BLA, including recall.

Once an approval is granted, the FDA may issue enforcement letters or withdraw the approval of the product if compliance with regulatory requirements and standards is not maintained or if problems occur after the drug or biologic reaches the market. Corrective action could delay drug or biologic distribution and require significant time and financial expenditures. Later discovery of previously unknown problems with a drug or biologic, including AEs of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the drug or biologic, suspension of the approval, complete withdrawal of the drug from the market or product recalls;
- fines, warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve applications or supplements to approved applications, or suspension or revocation of drug or biologic approvals;
- drug or biologic seizure or detention, or refusal to permit the import or export of drugs; or
- injunctions or the imposition of civil or criminal penalties.

Overview of the ICH E17 Guideline

The General Principles for Planning and Design of Multi-regional Clinical Trials, or the ICH E17 Guideline, provides some general recommendations in the planning and design of Multi-Center Clinical Trials ("**MRCTs**"). Some of those recommendations are as follows.

Subject Selection

In MRCTs, subject selection should be carefully considered to better understand and possibly mitigate potential sources of regional variability and their impact on trial results. Clear and specific inclusion and exclusion criteria, that are acceptable and can be applied across regions, should be included in the protocol.

To harmonize subject selection, uniform classification and criteria for diagnosis of the disease or definition of the at-risk population should be implemented, such as the use of relevant guidelines for disease definitions. When diagnostic tools are needed for the selection of subjects, these should be clearly specified including the degree to which local validated tools and qualified laboratories may be used. In particular, when subject selection is based on subjective criteria, the same methods should be used uniformly across regions. Even so, reporting of symptoms may vary by region and may lead to differences in the types of subjects included in the studies. This aspect should be considered in the planning stage, in order to implement training requirements and other strategies for potential mitigation of the impact.

Sample Size Planning

The key consideration for sample size planning, is ensuring sufficient sample size to be able to evaluate the overall treatment effect, under the assumption that the treatment effect applies to the entire target population, particularly to the regions included in the trial. MRCTs are usually stratified by region for both randomization and analysis. Consistency of treatment effects across regions is evaluated, and if clinically relevant differences are observed, there should be further exploration to determine if these differences can be attributed to differences in intrinsic or extrinsic factors. These considerations should be reflected in the overall design of the MRCT and will influence the sample size planning and allocation to regions.

- Overall Sample Size: The primary objective of an MRCT generally corresponds to an evaluation (estimation and testing) of the treatment effect averaged across all subjects in all regions of the MRCT. The overall sample-size is determined to ensure that this objective can be met. Examples of commonly defined treatment effects also used in MRCTs, are hazard ratios for morbidity or mortality, differences between treatment groups in average blood pressure levels (adjusted for baseline) and relative risks of either favorable or adverse events. The same general principles provided in ICH E9 for determining sample sizes of clinical trials apply to MRCTs. Two additional factors are particularly important in the MRCT setting; (i) the size of the treatment effect that is considered clinically relevant to all regions in the trial, and (ii) the expected variability of the primary outcome variables based on combining data across regions.

- Sample Size Allocation to Regions: The MRCT should be planned to include an evaluation of the consistency of treatment effects among regions, where consistency is defined as a lack of clinically relevant differences. Regional allocation should have a scientific basis (rather than arbitrary targets), should support the evaluation of consistency and should provide the information needed to support regulatory decisions. Sample size allocation to regions should take into consideration patterns of disease prevalence across regions, the size and expected accrual rate of each region, the intrinsic and extrinsic factors understood (or hypothesized) to influence treatment effects, the prevalence of those factors in each region and other logistical considerations thought to impact accrual. There is no uniformly acceptable or optimal approach to sample size allocation in an MRCT. Some approaches currently in use include:

  (i) Proportional Allocation: Allocation of subjects to regions in proportion to size of region and disease prevalence.

  (ii) Equal Allocation: Allocation of equal numbers of subjects to each region.

  (iii) Preservation of Effect: Allocation of subjects to one or more regions based on preserving some specified proportion of the overall treatment effect.

  (iv) Local Significance: Allocation of a sufficient number of subjects to be able to achieve significant results within each region.

(v) Fixed Minimum Number: Allocation of a fixed minimum number of subjects to a region.

- Pooled Regions and Pooled Subpopulations: Pre-specified pooling of regions or subpopulations may help provide flexibility in sample size allocation to regions, facilitate the assessment of consistency in treatment effects across regions, and support regulatory decision-making. The pooling strategy should be justified based on the distribution of the intrinsic and extrinsic factors known to affect the treatment response, and the disease under investigation and similarity of those factors across regions.

- Other Sample Size Consideration: The factors that influence sample size and sample size allocation should be agreed upon in advance with the different regulatory agencies governing the regions represented in the trial. There are some situations that do not fit into the framework for sample size allocation described above and where more flexibility will be required.

Choice of Endpoints

The Aspects of particular importance principles for endpoints selection to MRCTs are as follows.

- Primary Endpoint: The primary endpoint should be relevant to the target population. In MRCTs, this relevance needs to be considered for all regions in the trial and with respect to the various drug, disease and population characteristics represented in those regions. An ideal clinical trial endpoint is one that is clinically relevant, accepted in medical practice and sufficiently sensitive and specific to detect the anticipated effect of the treatment. For MRCTs, the primary endpoint, whether efficacy or safety, should satisfy these criteria as well as being acceptable to all concerned regulatory authorities, to ensure that interpretation of the success or failure of the MRCT is consistent across regions and among regulatory authorities. The primary endpoint of MRCTs should be one for which experience is already available in the participating regions. In cases where prior experience with an endpoint only exists in one or a subset of regions involved in the MRCT, its adoption as primary endpoint will require discussion and agreement with regulatory authorities regarding the basis for the evidence.

- Secondary Endpoints: Where possible, harmonization of secondary endpoints is encouraged to maintain the feasibility and improve the quality of trial conduct. However, in some cases, individual regulatory authorities may propose different secondary endpoints relevant to their interests and experience. Even in such cases, all secondary endpoints, including those selected only for a particular local stakeholder (e.g., regulatory authority), should be described in the protocol. It is in the interest of the sponsor to describe the specific advantages of the investigational drug, in terms of secondary endpoints as precisely as possible during the planning stage of MRCTs, to reduce the need for (and impact of) multiplicity adjustments for multiple endpoints, thereby improving the chance for successfully demonstrating the intended effect.

- Other Consideration: Although endpoints may not require formal validation, some endpoints may be subject to subtle differences in understanding, when used in different cultural settings. Approaches to minimize the impact of this variation in data collection and interpretation of the trial results should be described and justified in the study protocol. Endpoints that are only of interest to one or a few regions could be considered for a regional sub-trial of the MRCT. However, care should be taken to ensure that ascertainment of regional sub-trial endpoints do not hamper the conduct of the main trial. In particular, consideration should be given to the impact of additional burden to study subjects and study personnel, and the potential to induce reporting bias with respect to other endpoints, in determining whether regional sub-trials can be conducted or whether a separate trial is needed.

Privacy Rules and Safety Reporting

All sites participating in MRCTs should meet applicable quality, ethical and regulatory standards. Specifically, MRCTs should be conducted in compliance with ICH E6 GCP standards in all regions and sites, including making sites available for GCP inspections by regulatory authorities. The ICH E6 provides that the confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

Safety reporting should be conducted in accordance with ICH E2. When local regulations specify different requirements, such as timelines and criteria for expedited reporting, these should also be adhered to locally. The specific timeframe for safety reporting should be described in the protocol, and the investigators should receive sufficient training in accordance with ICH E6 and other relevant guidelines. In the case of MRCTs, important safety information should be handled both with adherence to any local regulations and in adherence to ICH E2A. Important safety information should always be provided to the relevant stakeholders (e.g., investigators, ethics committees) in a timely manner.